

## **Extensive ulcerative colitis and extraintestinal manifestations in a patient with HIV infection and significant CD4 T-cell lymphopenia**

Edouard LOUIS (1), Michel P. MOUTSCHEN (2), Pierre DE MARNEFFE (3), Raymonde MALHERBE (3), Thierry CLOSON (3), Michèle T'JEAN (3), Jean DEMONTY (2), Jacques BELAICHE (1)

*Department of (1) Gastroenterology and (2) Internal Medicine, CHU Sart-Tilman, Liège ; (3) Centre Hospitalier du Bois de l'Abbaye, Seraing, Belgium.*

### **ABSTRACT**

We report a heterosexual patient with HIV infection and a CD4 T-cell count of  $0.45 \times 10^9/L$  who developed mild ulcerative proctitis, sacroileitis and oligoarthritis. While he was treated with 5-aminosalicylic enemas, the patient rapidly developed severe pancolitis. An emergency colectomy without proctectomy was performed. A few months later, he suffered recurrence of ulcerative proctitis, aggravation of arthritic pain and developed anterior uveitis. All symptoms disappeared after proctectomy. There was no evidence for opportunistic infection or Kaposi's sarcoma. Antineutrophil cytoplasmic antibodies were positive and the HLA-B27 antigen was present. CD4 counts were lower during the phases of active disease than during remission. This case demonstrates that severe ulcerative colitis can occur in the presence of moderate T-cell defects. In view of a recent report of remission of Crohn's disease under comparable circumstances, it is possible that the extent of T-cell involvement in both diseases is radically different.

**Keywords :** Ulcerative colitis ; human immunodeficiency virus.

### **RÉSUMÉ**

**Rectocolite ulcéro-hémorragique sévère et manifestations extra-intestinales chez un patient infecté par le virus de l'immunodéficience humaine et ayant un déficit significatif en lymphocytes T CD4.**

Les auteurs rapportent le cas d'un malade hétérosexuel infecté par le virus de l'immunodéficience humaine avec  $0,45 \times 10^9/L$  lymphocytes T CD4 et qui a développé une rectocolite ulcéro-hémorragique distale légère associée à une sacro-iléite et à une oligoarthritis. Alors qu'il était traité par des lavements d'acide 5-aminosalicylique, sa rectocolite s'est rapidement aggravée et il a développé une pancolite sévère. Il a présenté des rectorragies importantes entraînant un choc hypovolémique, et une colectomie sans proctectomie a été réalisée en urgence. Quelques mois plus tard, la symptomatologie a repris sous la forme d'une proctite associée à une exacerbation des plaintes articulaires et à l'apparition d'une uvéite antérieure. Tous ces symptômes ont disparu après proctectomie et réalisation d'une anastomose iléo-anale. A aucun moment, une infection opportuniste ou un sarcome de Kaposi n'ont été mis en évidence. Les anticorps anti-cytoplasme des polynucléaires neutrophiles étaient positifs et le malade était HLA B27. Le taux des lymphocytes CD4 était plus bas durant les phases d'activité de la maladie que durant les rémissions. Ce cas montre qu'une rectocolite ulcéro-hémorragique sévère peut se développer en présence d'un déficit modéré des lymphocytes T. A la lumière de cas publiés de maladie de Crohn évoluant vers une rémission prolongée dans de pareilles circonstances, il est possible que l'implication des lymphocytes T dans le développement de ces deux affections soit radicalement différente.

**Mots-clés :** Rectocolite hémorragique ; virus de l'immunodéficience humaine.

### **ABBREVIATIONS**

CD : Crohn's disease.  
HIV : human immunodeficiency virus.  
IBD : inflammatory bowel disease.  
PMN : polymorphonuclear neutrophils.  
UC : ulcerative colitis.  
CRP : C reactive protein.  
ESR : erythrocyte sedimentation rate.  
CMV : cytomegalovirus.  
s IL-2R : soluble interleukin-2 receptor.

Exacerbation of local T-cell responses has been demonstrated in inflammatory bowel disease (IBD) (1-3). However, it remains to be determined if the disease is due to intrinsic abnormalities of immunoregulatory mechanisms or if T-cell activation is secondary to sustained stimulation due to defects in the mucosal barrier. Furthermore, the respective participation of non-specific inflammatory responses versus T-cell mediated immunity in tissue damage is not precisely established. Therefore, specific features of IBD in patients with selective defects of T-cell mediated immunity are of major interest. We describe the severe course of ulcerative colitis (UC) in a patient with HIV infection and significant drop in CD4 T-cell counts.

## CASE HISTORY

A 35-year-old heterosexual man presented to CHBA-Seraing Hospital in January 1992 with rectal bleeding and articular pain. Proctorrhagia without diarrhea had been present since July 1991. Migratory arthralgia involving the left hip, the toes and the back appeared in November 1991. The patient presented with general malaise and fever up to 38°C. Sigmoidoscopy showed ulcerative lesions confined to the rectal mucosa. Rectal biopsy specimen revealed mucosal ulceration, crypt abscess formation in the mucosal and submucosal layers and prominent mixed inflammatory reaction with polymorphonuclear neutrophils (PMN) and lymphocytes. There were no granuloma, no viral inclusions and no evidence for mycobacterial infection. Laboratory examination revealed a prominent inflammatory reaction : fibrinogen 6.87g/L, C-reactive protein (CRP) 67 mg/L, erythrocyte sedimentation rate (ESR) 63 mm/h. Hemoglobin was normal at 13.3 g/100 mL. Because of high risk sexual behavior from 1984 to 1988, antibody testing for HIV was proposed to the patient and revealed positive. The total lymphocyte count was  $1.53 \times 10^9/L$  (N :  $1.00-4.80 \times 10^9/L$ ), the total CD4 T-cell count was  $0.45 \times 10^9/L$  (N :  $0.70-1.10 \times 10^9/L$ ) and the total CD8 T-cell count was  $0.73 \times 10^9/L$  (N :  $0.50-0.90 \times 10^9/L$ ). HIV-1 p24 antigen was negative. The patient was classified as having mild ulcerative proctitis (4) and treatment with 5-aminosalicylic enemas (Colitofalk®) was started. Piroxi-cam (Feldene®) 20 mg/day was given for the arthralgia. The patient improved and remained stable during several weeks.

In March 1992, he suffered sudden and massive rectal bleeding with severe hypovolaemic shock. Emergency colectomy without proctectomy was performed. The entire colonic mucosa appeared ulcerated and haemorrhagic with prominent infiltration by PMN. No histological evidence of Kaposi's sarcoma, lymphoma or opportunistic infection, including cytomegalovirus (CMV) and amoebiasis, was detected. No anti-CMV IgM was found in the serum. The patient progressively improved and was discharged from the hospital in May 1992. When he left the hospital, a significant inflammatory reaction was still present (fibrinogen : 5.55 g/L, ESR : 65 mm/h). The total CD4 T-cell count was  $0.62 \times 10^9/L$  and the total CD8 T-cell count was  $1.02 \times 10^9/L$ .

From May to December 1992, the general condition kept improving slowly. Occasional rectal bleeding was still present. The patient described the persistence of moderate pain in the knees, the ankles and the back. Inflammatory reaction never subsided. CD4 T-cell counts remained between  $0.50$  and  $0.60 \times 10^9/L$ . In January 1993, rectal bleeding and articular pain rapidly worsened and the patient was admitted at CHU Sart-Tilman Hospital. Rectoscopy showed a fragile and inflamed mucosa with pseudopolyps. Biopsy confirmed typical histology without evidence of opportunistic infection, lymphoma or Kaposi's sarcoma. There was also a large ulceration in the anal canal which was thought to be infectious, but serology for *Treponema pallidum* was negative and biopsies showed non specific features. That ulceration healed spontaneously. Radiology demonstrated left sacroileitis. Juxta-articular osteopenia without erosion was observed at the level of the left knee and of the left ankle. Effusion was also present in the left knee. Soon after, the patient developed ocular discomfort and was diagnosed with acute anterior uveitis. The biological investigation revealed the presence of the HLA-B27 antigen. Anti-neutrophil cytoplasmic antibodies were positive and rheumatoid factor was negative. Serology was negative for *Salmonella*, *Yersinia* and *Chlamydia*. There was an important inflammatory reaction with fibrinogen 5.36g/L, CRP 29 mg/L and ESR 60 mm/h. Soluble interleukin-2 receptor (sIL-2R) was increased at 132 pmol/L (N : 50-100).  $\beta_2$  microglobulin was normal at 1.9 mg/L. Total CD4 T-cell count was  $0.42 \times 10^9/L$  and total CD8 T-cell count was  $1.18 \times 10^9/L$ . The proportion of circulating T-lymphocytes expressing the IL-2 receptor  $\alpha$  chain (IL-2Ra - CD25) was low at 10 % (N : 13-24 %), the proportion of CD8 T-cells positive for CD57 was markedly increased at 60 % (N : 19-34 %). IgG were increased at 29.18 g/L (N : 8.2-17 g/L) due selectively to the IgG1 subclass measured at 23.63 g/L (N : 5.96-8.93 g/L). Circulating HIV p24 antigen was detected at 8 pg/mL. Because of HIV p24 antigenemia, zidovudine therapy (500 mg/day) was introduced.

In February, proctectomy with ileoanal reconstruction were performed. The patient rapidly improved and noted complete remission of articular pain. In April 1993, the inflammatory reaction had subsided (CRP 8 mg/L). CD4 counts were stable at  $0.52 \times 10^9/L$ . The level of IgG had fallen to 17.19 g/L (IgG1 : 12.8 g/L). sIL-2R was normal at 89 pmol/L. The proportion of CD8 T-cells positive for CD57 was stable at 60%. HIV p24 antigen was still positive at 15 pg/mL. In May, ileostomy was closed and the continuity between terminal ileum and anus was

reestablished. In September 1994, while he still had a similar biological profile, some lymphocyte function tests were performed. They showed a significant decrease in proliferation to the mitogen BMA030 : 12 790 cpm compared to 21 752 cpm (95% confidence interval: 14 547-28 955) in controls. The patient is currently free of any rectal bleeding or articular pain. His general condition is improving.

## DISCUSSION

We have described the course of an ulcerative colitis in an HLA-B27 positive patient infected with the HIV-1 virus and presenting with a significant decrease of CD4 T-cells. Few cases of inflammatory bowel disease in HIV-infected subjects have been reported so far (5-8). In several cases, homosexual patients with chronic HIV-infection were initially diagnosed as having UC and were ultimately found to present Kaposi's sarcoma of the bowel (9, 10). James (5) described the complete remission of a long-standing Crohn's disease (CD) in an HIV-infected patient when his CD4 T-cell counts reached  $0.41 \times 10^9/L$ . This was further confirmed by other case reports from France (8). Franke et al. (6) reported severe UC in a homosexual patient with chronic HIV-1 infection and CD4 T-cells at  $0.50 \times 10^9/L$ . Although the diagnosis was not histologically established in Franke's report, there was a strong clinical presumption given the rapid response to prednisone and mesalazine. In another report, an heterosexual patient with lower CD4 T-cell counts ( $0.22 \times 10^9/L$ ) developed acute UC after amoebic dysentery. The diagnosis was confirmed by the biopsy and the response to prednisone and mesalazine (7).

In the present case, the diagnosis of ulcerative colitis has been firmly established by typical histological findings, absence of evidence for CMV infection, amoebiasis and Kaposi's sarcoma and negativity of stool cultures. Several non-specific abnormalities often associated with UC such as the positivity for antineutrophil cytoplasmic antibodies (11), increased serum IgG1 (12), increased proportion of circulating CD8 T-cells expressing CD57 (13) and increased level of sIL-2R (14) were also found in our patient. However, the diagnostic value of these non-specific features is low in the present case because several of them have also been described in HIV patients or infectious colitis. Moreover, this patient had a rather severe disease. First, the disease, initially localized to the rectum, rapidly involved the entire colonic mucosa. Classically, such a rapid extension of the disease is found only in 5 to 10 % of the cases (15). Second, he had a severe manifestation of this extensive colitis with major bleeding leading to an emergency colectomy. The use of a classical treatment of severe UC with IV steroids could have been considered in such a situation. However the lifethreatening bleeding with hypovolemic shock motivated the gastroenterological team to perform a colectomy. Third, the extent of extraintestinal manifestations was unusually severe with anterior uveitis and major limitation of motion due to sacroileitis and migratory oligoarthritis. Ocular manifestations are found in only 5 % of patients with IBD and are associated with particular severity (16).

Our patient did not develop any opportunistic infection before the diagnosis of EBD, however it is important to note that his CD4 T-cell counts were in the same order of magnitude than those associated with remission of CD in James' study (5). Furthermore, it is well established that striking functional defects of CD4 T-cells can be observed in asymptomatic HIV-infected patients before the collapse of CD4 counts (17, 18). Indeed our patient presented a mild defect in lymphocyte proliferation to the mitogen BMA030. This suggests that a moderate CD4 T-cell defect does not inhibit the course of UC and indicates that the involvement of T-cell mediated immunity in CD and UC might be fundamentally different. This hypothesis is also supported by studies on T-cells characteristics and activity in IBD. Phenotypic signs of T-cell activation in situ are less prominent in UC than in CD (14), furthermore stimulated-interleukin-2 (EL-2) secretion by intestinal T-cells is more impaired in UC than in CD (19,20). A recent study of the lymphokine secretion by CD4 + lamina propria lymphocytes in CD and UC showed significant differences (21). There was an increased production of IFN- $\gamma$  in CD and of Interleukin-5 in UC. Moreover preliminary data indicate that apoptosis of mucosal T lymphocytes is increased in UC and decreased in CD (Fiocchi C, personal communication). Recently the IL-2 knockout mice model was developed. Some of these mice develop progressive colonic inflammation resembling UC in many aspects (22). Thus, although the amount of CD4 + T lymphocytes is not significantly different in CD and UC, activation, lymphokine production and apoptosis may be different leading to dramatically different effects of their decrease and functional alterations due to HIV infection.

It remains to be established if the severity of UC in this patient was fortuitous or facilitated by HIV-related factors. The short-term treatment of arthralgia by piroxicam could also have been involved in the extension of the disease, from November 1991 to March 1992 (23), however it is not likely to have influenced the second recurrence in December 1992, because by that time it had been stopped for several months. A switch of CD4 T-cells to the TH2 phenotype (secretion of IL-4, IL-5, IL-6 and IL-10) is described in HIV infection (24) and could modify the regulation of local inflammatory responses. The severity of extra-intestinal manifestations could also be related with HIV infection since the association of this infection with other musculoskeletal syndromes such

as Reiter's syndrome has been well established, especially in HLA-B27 patients (25).

The influence of UC on the course of HIV infection has to be addressed. It is interesting to note that the CD4 T-cell counts were significantly lower when the disease was diagnosed, rose after colectomy, and decreased again during the recurrence of the symptoms in December 1992. Furthermore, the appearance of circulating HIV p24 antigen in this patient was unusual given the absence of major immunodeficiency. It may indicate that the immune activation associated with UC (as reflected in this patient by the increased levels of sIL-2R) might enhance HIV replication and accelerate the course of the disease.

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